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Late Malignant Transformation of Dormant Ganglioneuroma?

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Key words: multifocal neuroblastoma; late relapse; solitary metastasis; chemotherapy resistance

M. Moschovi, MD (Pediatric Oncology Registrar)

The patient (VG) is a 7-year old boy who presented at another institution with pain and swelling in the middle of the right tibia, which had been present for 5 months. A bone scan revealed increased uptake of 99 m-Tc-diphosphonate confined to the leg. All other bones were negative. A biopsy was performed and the histological picture was that of a neuroblastoma.

The patient was transferred to our oncology unit shortly thereafter. His family history showed no clustering of neoplasms. Initial workup revealed a normal-appearing young boy, well developed, and in good health. He had no palpable masses nor any other pathological clinical sign. There were normal vales for the usual blood and serum chemistry studies. The urine VMA was normal. Bone marrow aspiration was normal. The usual imaging studies were performed.

May we now see the histopathology?

D. Arvantis, MD (Consultant Pathologist)

The tissue was composed of small, round, or slightly elongated cells with scant cytoplasm but with formation of typical neuroblastoma rosettes (Fig. 1). It was not difficult to differentiate this lesion from other small, round cell tumours [1].

F. Tzortzatou-Stathopoulou, MD, PhD (Assoc. Prof. Pediatric Oncology)

A solitary bone metastasis and the age of the patient are quite unusual for neuroblastoma [2]. Do you think that it could be any other small round cell tumor?

Dr. Arvanitis. There is no doubt that this is a metastatic stroma-poor undifferentiated neuroblastoma, because the tumor, in addition to typical neuroblastoma rosettes, was positive for NSE and negative for glycogen.

Dr. Moschovi. An extensive search for other sites of disease was undertaken. Dr. Hadjigeorgi, what did you find?

Ch. Hadjigeorgi, MD (Pediatric Radiologist)

The 99 m-Tc MDP bone scan showed only increased activity in the middle of the right tibia (Fig. 2). Subsequent CT scans of the abdomen and pelvis demonstrated small tumors in both adrenals, 2 cm in diameter on the left and 1.5 cm on the right with significant contrast enhancement. A CT of the chest revealed a thoracic paraspinal mass on the right $4.5 \times 3.5 \times 3.0$ cm with central calcification (Fig. 3). There were no pulmonary metastases or lymph nodes in the mediastinum.

Increased uptake of 123-I MIBG was found in both adrenals, the site of the thoracic tumour and the middle of the right tibia (Fig. 4). There was no other bone involvement.

Dr. Moschovi. The patient started chemotherapy for stage IV neuroblastoma with vincristine, cyclophosphamide, carboplatinum, etoposide, and dacarbazine (DTIC) in the usual doses. The response as evaluated by CTs and MIBG was not satisfactory after 5 months of this therapy. A complete excision of the left adrenal (the bigger mass) was performed, and the histology showed it to be a ganglioneuroblastoma. He continued chemotherapy for 1 year, at which time the MIBG appeared negative and the child appeared to be in complete remission.

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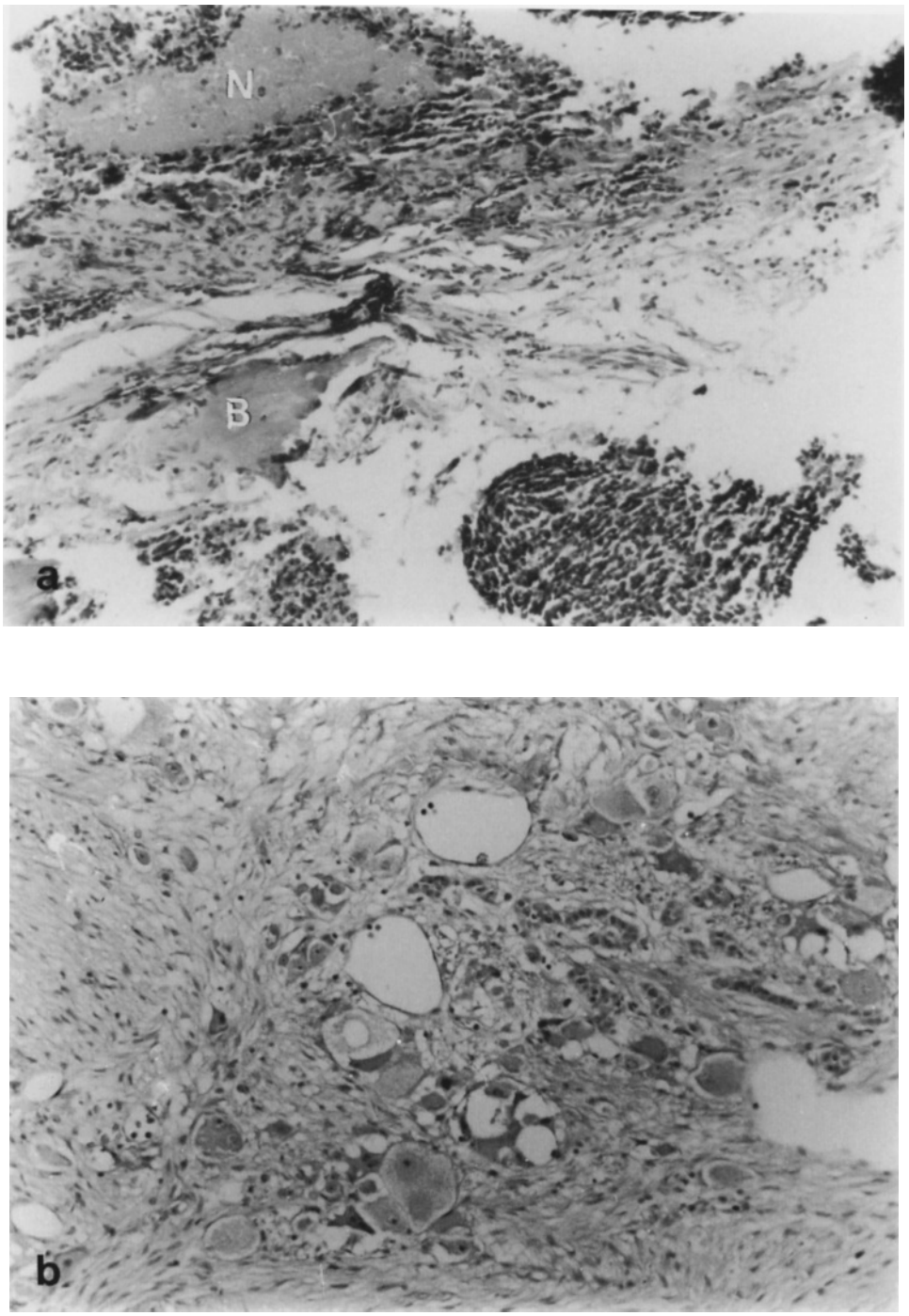

Fig. 1. (a) Metastatic neuroblastoma of tibia (H.E. × 2.5). N: necrotic focus, B: bone spicule. (b) Ganglioneuroblastoma of adrenal, with mature ganglion cells and immature elements (H.E. × 10).

Dr. Tzortzatou-Stathopoulou. This patient presented with a single bone metastasis associated with multifocal neuroblastoma tumours (i.e., in both adrenals and in the thoracic sympathetic chain). This constellation of clinical findings and the age of the patient are certainly exceptional. The biologic behavior also is a great interest in that the tumors were resistant to treatment. The adrenal showed active neuroblastoma after six courses of aggressive chemotherapy with only a small amount of differentiation toward ganglioneuroma. It took >15 courses of therapy before the MIBG scans returned to normal. Some questions are: Are these multifocal tumours multiple primary tumors or metastatic foci? How long should one treat such patients? What should the "stop-treatment"

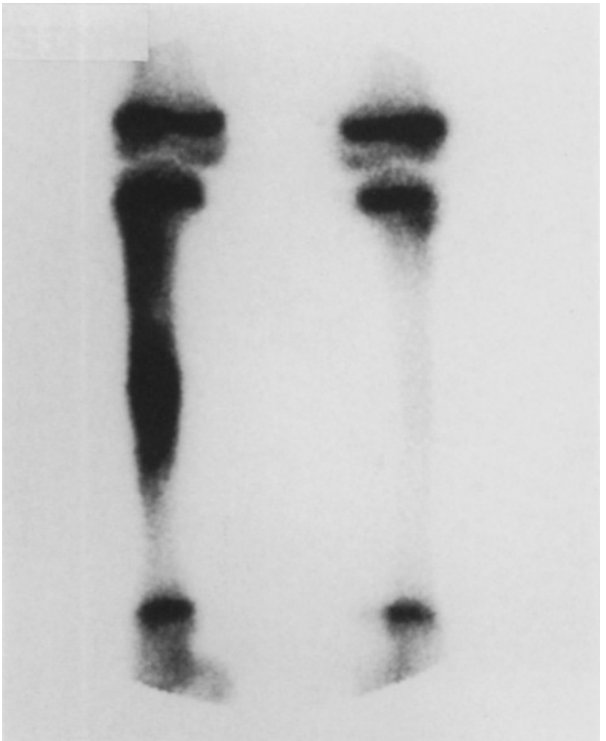

Fig. 2. 99 m-Tc MDP bone scan. Increased activity in right tibia.

criteria be? Do cases like this one have a better prognosis because only one bone lesion was identified at diagnosis, as has been suggested [3]?

It is reasonable to propose that the tumors represent synchronous development of tumours and not metastases from one adrenal to the contralateral organ or to the thoracic paraspinal chain. This reasoning draws support from the observation that the individual tumors were small and wide dissemination was not present. They all also remained confined to their respective organs of orgin without crossing the midline. They therefore appear to have been separate lesions. Bilateral adrenal neuroblastoma and other multifocal tumors, although known, are not common and reports are infrequent [4–10]. There are <50 reported cases of multifocal neuroblastoma noted in the literature [11]. These tumors usually involve both adrenal glands or other sites in which neuroblastomas normally occur. They may be present synchronously or metachronously and are most often reported in families with a history of neuroblastoma [12]. Our patient had no family history of neuroblastoma or any other tumor. Metachronous lesions have been reported many years following removal of the initial tumor [13]. Usually, patients with multifocal neuroblastoma seem to have a good outcome on the basis of their favorable biological behavior. It has been recommended by Brodeur et al. [14] that patients with multifocal disease be identified as such in the International Neuroblastoma Staging System. The patient is staged ". . . according to the most advanced extent of tumor . . . followed by a subscript letter M (e.g., 3_M)."

There may be a clinical form of neuroblastoma that, despite originating in multiple sites, tends to follow a quiescent course and not to spread widely [4]. Surgery as the only treatment yields a favorable outcome. Our patient, however, had a bone metastasis that obviously called for systemic therapy rather than surgery alone.

The age at diagnosis and the multifocality raise another possibility. This patient could represent late relapse after a long period of quiescence of multifocal disease [15]. This has been reported, with delays of many years before recrudescence. Among 24 cases of late recurrences in neuroblastoma, 13 were well documented and were reviewed by Hata et al. [6]. Eight of them were infants <1 year of age at diagnosis. It is known that spontaneous regression of the disease can be observed in some infants, with occasional reports of late recurrence. In some of the other five cases, the clinical course suggested a malignant change of a ganglioneuroma to a neuroblastoma. Other authors have also reported late recurrences after as long as 52 years of apparent dormancy [15–18]! No significant response to treatment was observed in these patients; they suffered late relapses and died.

Extending this construct further, there is the intriguing thought that this patient perhaps as a baby originally had a favorable kind of neuroblastoma according to the expanded concept of Stage IV-S disease [19]. Going on with this hypothesis, the lesions then regressed and remained dormant for years. For reasons unknown—perhaps a "second hit" to use the Knudson model [20]—the tumor became active again, this time with a frankly malignant process that gave rise to distant metastases.

That seems to have been the sequence in an 18-year old girl, completely asymptomatic, who suddenly developed a nodule on the dorsum of the foot. This was excised and found to be a ganglioneuroblastoma. Staging followed, and she was found to have metastatic neuroblastoma to which she eventually succumbed. It was postulated that she had had a IV-S skin lesion that disappeared spontaneously, only to reappear with explosive consequences [G.J. D'Angio, pers. comm.].

Perhaps that sequence occurred in our patient, since none of the tumors were at an advanced stage when discovered. His prognosis in any case remained guarded, despite the remission he seemed to be enjoying.

Twenty months after diagnosis the patient presented again with a local relapse in the right tibia extending to the femur. He received local radiotherapy without response and died 2 years after diagnosis with disseminated disease, mainly in the liver.

We can now turn to some of the questions asked earlier.

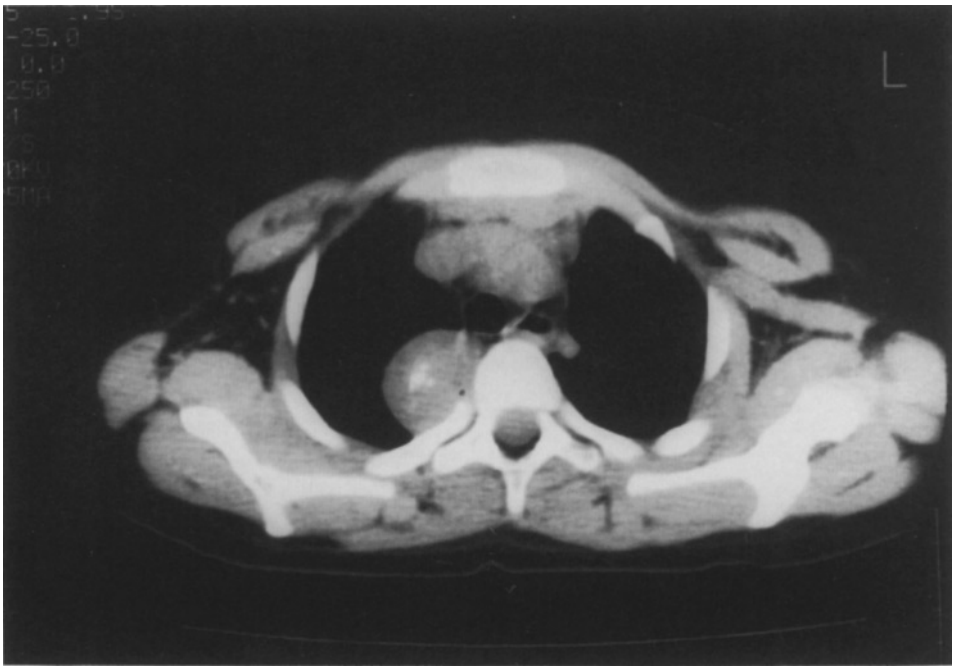

Fig. 3. CT scan of the chest. A thoracic paraspinal mass with central calcification is visible.

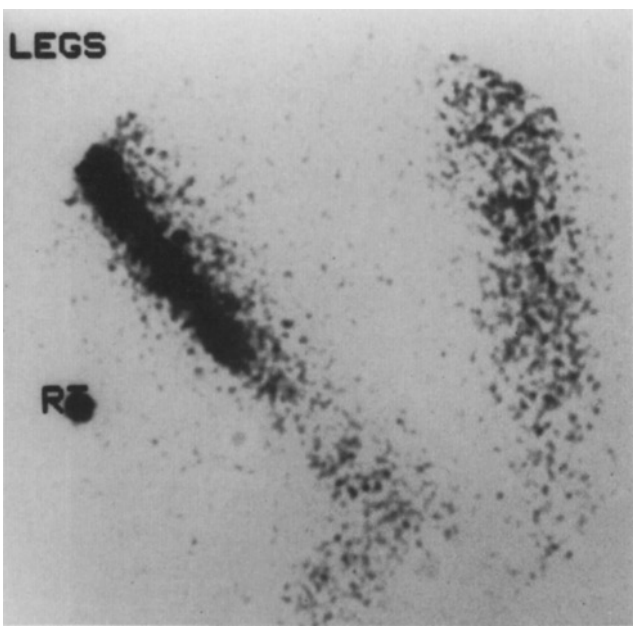

Fig. 4. 123-I MIBG. Increased uptake was found in the middle of the right tibia.

We believe that the case presented here had multifocal primary tumors and not metastatic disease. This seems relatively clear since the patient had bilateral adrenal primary neoplasms. The tumors of multifocal neuroblastoma present synchronously or metachronously, usually at young age, can lie dormant for several years and finally give rise to late recurrences of high malignancy, which seem to be resistant to chemotherapy. There is no definite "stop-treatment" criterion. Despite the single recurrence site and the intense chemotherapy the patient received, the disease was not brought under control. It thus would not appear that a better outcome can be assumed when recurrence sites are few in number or even solitary as in this boy.

Our experience with this patient serves to emphasize the protean manifestations of this treacherous and at times relentless disease.

Addendum

Neuroblastoma tissue had been obtained from the primary adrenal tumor of the patient undergoing surgery after chemotherapy and it was frozen until the time of analysis. Since it has been reported that genomic amplification of N-myc is not affected by chemotherapy [21,22], the N-myc copy number was established, and differential PCR revealed a nonamplified N-myc (Fig. 5). However, absence of N-myc gene amplification does not necessarily reflect a good outcome, as the clinical course of our patient with low N-myc copy number showed. Thus when N-myc gene amplification is not present, other predictive factors should be evaluated before prognosis is assigned [23,24].

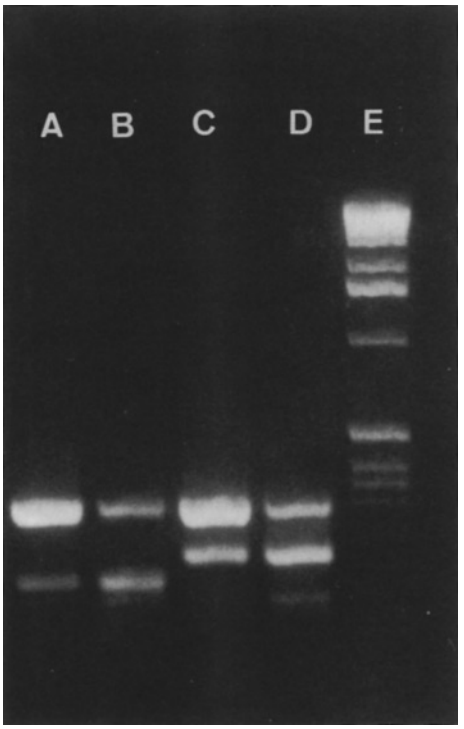

Fig. 5. N-myc differential PCR. The primers used besides N-myc (300 bp product), were INFγ (150 bp product) and N-ras (200 bp product) as reference one-copy genes. **A:** n-myc/INFγ positive control, **B:** N-myc/INFγ patient DNA, **C:** N-myc/N-ras positive control, **D:** N-myc/N-ras patient DNA, **E:** Size marker N-myc:INFγ ratio of patient DNA ~ 1

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